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Research Article

Development and optimization of Lamotrigene containing Liposomal Transdermal Patches

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Abstract

Antiepileptic drugs are generally available as tablets for oral administration, but this can pose problems for patients who are unable to consume medications orally. Transdermal drug delivery is useful in such cases. There is therefore an unmet need for enhancement techniques with the potential of delivering high dose medications across the skin. The transdermal route of drug administration ensures systemic delivery of drug by applying a drug formulation onto intact as patch on healthy skin thus ensuring sustained drug release and bypass of first-pass metabolism. Transdermal drugs significantly deliver molecules in a potent quantity that overcome the conventional problems of oral dosing. Thus, the objective of the proposed study is to develop lamotrigene-loaded transdermal patch an effective substitute for the existing maintenance therapies used for controlling epileptic seizures. We embarked on the transdermal delivery of lamotrigene upon this scientific basis.

Keywords: Lamotrigene, Antiepilepsy, Transdermal patch, Liposomes, Vesicular system

INTRODUCTION:

Epilepsy is a disorder of the brain characterised by an enduring predisposition to generate epileptic seizures and by neurobiologic, cognitive, psychological and social consequences of this condition[1]. The epilepsy associated seizures are distinct to a person and undetectable sometimes and thus require special attention. Seizure is an event of transient occurrence of signs or symptoms due to abnormal, excessive or synchronous neuronal activity of the brain which can vary from short to long periods of vigorous shaking[2]. Skin is the outer tissue of the human body. People are very sensitive to appearance of their skin. Skin is the largest organ of human body in terms of weight and surface area both. The skin is the heaviest single organ in the body[3]. Skin varies in thickness, color, and texture. There are two major types of skin: Thick and hairless, found on the palms and soles of feet in areas that are heavily used. Thin and hairy, found over most of the body. Skin is a complex organ system perform many important functions such as act as protective barrier against external organisms, keep temperature control, senses our surroundings, eradicate wastes, and synthesizes Vitamin D. Skin also maintain the body in homeostasis. Skin also stores fat and water, and plays a role in immunity from disease[4-5]. Oral route is the most preferred route fastens in patient fulfilment; though, oral administration is more prone to hepatic first pass metabolism required higher dose of drug. Additional, gastric irritation is the major restrictions for the presence of surfactants in the lipid-based formulations[6] concurrently the distribution of drug throughout the body can lead to obligatory side effects. Hence the non-invasive, non-paining, non-irritating topical delivery of formulation is an alternate technique associated with several advantages such as delivery of drug to specific site of action with reduced systemic toxicity, avoidance of first pass metabolism and gastric irritation, increasing release rate of drug from formulation to get better percutaneous absorption and for a moment topical application related to increase bioavailability with sustained release profile[7-8]. Further its advantages illustrate, traditional transdermal formulations, viz: ointments, creams, lotions are in concurrence with many disadvantages such as sticky nature, lack of spreadibility, stability issue, etc., ultimately leading to patient incompliance. Modernization of transdermal delivery by the formulation revealed transparent gel and emulgel with greater patient agreement and better efficacy. Therefore, these formulations are acquisition interest both in cosmetics industries, as well as in pharmaceutical industries. Despite lots of advantages of gel and emulgel formulations, delivery of hydrophobic drug still remains a big obstacle to cross over. Furthermore, skin penetration through stratum corneum is also a great concern to the researchers for the systemic activity of the transdermal delivery[9]. The topical drug delivery offer a direct accessibility to the skin as a target organ for diagnosis and treatment without fear of undergoing first pass metabolism. Topical drug administration is a localized drug delivery system anywhere in the body throughout ophthalmic, vaginal, rectal and skin as topical routes. Skin is one of the most readily available organs

on human body for topical administration and is the main route of topical drug delivery system. Drugs are administered topically for their action at the site of application or intended for systemic effect[10]. Dermatological products applied to skin are varied in formulation and range in consistency from liquid to powder but the most popular products are semisolid preparation. The semisolid preparations transparent gels has expanded both in cosmetics and in pharmaceutical preparations. The development of dosage forms for topical drug delivery is one surrounded by the many challenging areas to the formulation scientists. Various layers of skin (epidermis, dermis and hypodermis), the stratum corneum of epidermis is the effective rate limiting hurdle to percutaneous drug transport, as this layer is made up of dead cells of corneocytes which lack nuclei and organelles[11]. Other advantage of topical preparations are avoidance of the risks and inconveniences of intravenous therapy and of the varied conditions of absorption, like pH changes, presence of enzymes, gastric emptying time[12]. The topical drug delivery system is normally used where the others system of drug administration not succeed or it is mainly used in fungal infection. Human skin is a large and easily accessible organ offers ideal and multiple sites to administer therapeutic agents for both local and systemic actions. Emulgel is emulsions, either of the oilin-water or water in oil type, which are gelled by mixing with a gelling agent. Several antifungal agents are available on the market in different topical preparations (e.g. creams, ointments, and powders for the purpose of local dermatological therapy). One of these antifungal agents is Itraconazole, which has both antifungal and antibacterial properties. It applied locally in mild dermatophyte and cutaneous infections[13]. The gellified emulsion was stable and better vehicle for hydrophobic or water insoluble drugs. Such emulsion is either of the oil-in-water or water-in-oil type, which was prepared gelled by mixing in a gelling agent. Oil-in-water emulsions are generally useful as water washable drug bases and also for general cosmetic purposes, while water-in- oil emulsions are employed more widely for the treatment of dry skin and emollient applications. The topical drug delivery system diffuses drug out of the delivery system reaches to the site of action and get absorbed by the skin. The release rate of the drugs from topical preparation is depending directly on the physiochemical properties of the carrier and the drug employed. Lamotrigine is a new anticonvulsant having carbamazepine-like profile: modifies aximal electroshock and decreases electrically evoked as well as photic after-discharge duration[14]. Lamotrigine is properly absorbed orally and metabolized completely in liver. Its t½ is 24 hr, but is reduced to ~16 hr in patients receiving phenytoin, carbamazepine or phenobarbitone. Lamotrigine is indicated as adjunctive remedy for the subsequent seizure kinds in patients ≥2 years of age: partial seizures, number one generalized tonic-clonic seizures, and generalized seizures due to Lennox-Gastaut syndrome. Lamotrigine probably prevents seizures and stops temper symptoms thru stabilizing presynaptic neuronal membranes and stopping the discharge of excitatory neurotransmitters along with glutamate, which contribute to seizure interest[15].

MATERIAL AND METHODS:

Determination of absorption maxima (λ_{max}): The absorption maxima of drug (Lamotrigine) determined by scanning drug solution in double beam ultraviolet spectrophotometer between 200 to 400 nm wavelengths at dissolution medium (phosphate buffer pH 7.4) solution (Shimadzu, UV-1800, Shimadzu Corporation, Kyoto, Japan).

Preparation of calibration curve of Lamotrigine: Accurately weighed required quantity of drug was dissolved in 50 ml of dissolution medium containing Phosphate buffer pH 7.4 in 50 ml volumetric flask with the help of sonication in bath sonicator for 20 min. The absorbance of 5 µg / ml, 10 µg / ml, 15 µg / ml, upto 40 µg / ml respectively solution was measured separately at 305 nm for Phosphate buffer pH 7.4. The absorbance was measured and standard curve was plotted between absorbance vs. concentration[16].

Preparation of Liposomes formulations:

Preparation and characterization of liposomes containing drug: The liposomes containing lamotrigine drug will be by thin film hydration method with various lipohillic phospholipid molecules i.e. soyalecithine, cholesterol etc. The prepared liposomal formulation characterized for optimized the best formulation by such parameters i.e. zeta potential, entrapment efficiency, size and polydispersity index and In vitro release study etc (Table 1).

Development of transdermal patch: The obtained liposomes were stored under normal room temperature and transdermal patches were prepared using solvent casting method. The transdermal films containing lamotrigene were formulated by using different polymeric combinations of Poly vinyl alcohol and Poly vinyl pyrrolidone. The casting films were prepared by polymer mixture was prepared by dissolving weighed quantities of polymers in water. The drugs were dissolved in methanol as solvent, which added to the prepared polymeric (PVA:PVP; 60:40) solution with Propylene Glycol 400 (10% w/v) as plasticizer and Tween 80 (5% v/v) were added respectively. The solution of mixture (20 ml) was poured into petri plates, kept it in the hot air for drying and kept it in the hot air for drying upto 24 h for solvent evaporation. The patches (F. codes; TP1, TP2, TP3, TP4) were removed by peeling and cut into square dimension of 2 cm × 2 cm (4 cm^2). These patches were kept in desiccators for 2 days for further drying and wrapped in aluminum foil, packed in self-sealing covers[17].

Characterisation of liposomal transdermal patch:

Physical appearance: The physical appearance of transdermal patches was visually inspected for its color, clarity, flexibility, and smoothness.

Thickness: The thickness of transdermal patches was measured using screw gauge at different sites.

Weight uniformity: The weight variation of patch was obtained by weighing of three patches randomly selected from the batch of formulation.

Folding endurance: The Folding endurance test of patch was carried out by folding the patch at the same point upto "n" number of times, till it may broken.

Tensile strength: The prepared patch strips as declared dimension should be free from air bubbles were hold between two clamps at a distance of 3cm. The patches were pulled at top clamps with a rate of 100 mm/min force and patch elongation were measured at the time of film broken. Formulae are:

% Elongation at break = Increase in length / Original length × 100

Swelling ratio: The effect of polymer combination during application was performed by swellability of the patch. The swelling properties of transdermal patches were found by keep in double distilled water in petri dish, and identified swelling nature of patch upon contact with water for specified time. The degree of swelling (S%) is calculated using the formula given below.

$$S (\%) = Wt - Wo / Wo \times 100 \ldots\ldots\ldots\ldots(4)$$

Where,

S= percent swelling,

W_t= weight of patch at time t,

W_o = weight of patch at time zero.

Surface pH: The patches were kept in 0.5 ml double distilled water and allowed to swell for 1 h. The surface pH of prepared patches was calculated by combined glass electrode at the surface of the patch for 1 minute[18].

Drug content: The drug content was determined for identified the specific quantity of drug presence in prepared patch. Patch (2 cm2) was cut into pieces and keep into a 100 ml volumetric flask containing 100 ml phosphate buffer pH 7.4 for 24 hours with occasional shaking. After shaking, filtered and prepared suitable dilution with phosphate buffer pH 7.4. The blank was prepared with drug-free patch. The solutions were observed by UV spectrophotometer at wavelength 305 nm for lamotrigene.

in-vitro diffusion studies: The drug release study of liposomes containing transdermal patch content was studied by dialysis method in phosphate buffer pH 7.4 solution or artificial skin pH medium using laboratory prepared Franz diffusion cell containing 35 ml of dissolution medium. Before experiment, the patch was kept into the receptor compartment screwed with two clamps at each end and stirred continuously at 100 rpm. The donor compartment was kept in contact with a receptor compartment and the temperature was maintained at 37±0.5°C. The receptor compartment was closed to prevent evaporation of the dissolution medium. The solution on the receptor side was stirred by externally driven teflon coated magnetic bars. At predetermined time intervals, 5 ml of solution from the receptor compartment was pipette out and immediately replaced with fresh 5 ml phosphate buffer pH 7.4. Samples were withdrawn at regular time intervals, and the same volume was replaced with fresh dissolution medium. The amount of drug entrapped in the vesicle was then determined by filtering it and the drug content was determined using UV-Vis spectroscopy at 305 nm[19]. Calculation of percentage drug release was done using the formula:

$$\%\ drug\ release = \frac{(Conc.\ of\ drug\ (in\ mg) \times Volume\ of\ receptor\ compartment) \times 100}{Label\ claim\ (amount\ of\ drug\ in\ donor\ compartment)}$$

RESULTS AND DISCUSSION:

The absorption maxima of drug (Lamotrigine) at 305 nm for Phosphate buffer pH 7.4. and the standard curve was plotted between absorbance vs. concentration and showed linear in nature with r2 value 0.999 (Figure1). The particle size distribution of lamotrigene containing liposomes assessed using zeta-sizer showed an average particle size of 122.11±1.12 to 131.31±1.08 nm with double in layer and polydispersity index were 0.213±0.02 to 0.229±0.11 (Figure 2). The size was analysed to be sufficiently small to penetrate the pores of stratum corneum. All liposome containing lamotrigene formulations and their ionic interaction with the biological membrane, the zeta potential was analysed to be -20.12±1.02 to -23.91±1.01 mV. The zeta potential directly indicates the surface charge of the lipid nanocarrier. Thus the zeta potential of a stable dispersion of liposome (Figure 3). The entrapment efficiency of all liposomes ranged between 63.05±0.8% to 83.17±1.04%. The maximum entrapment was found to be 83.17±1.04% for the liposome formulation LLP4 (Table 2). The entrapment efficiency of liposomes was dependent on the concentrations of polymeric solution varied used for preparation of proposed formulation.

Characterisation of liposomal transdermal patch

The proposed liposomal transdermal patch were flexible, smooth, opaque, non sticky in nature. The thickness of various transdermal patches prepared varied between 0.22±0.02 to 0.27±0.01 mm The difference in thickness showed very less standard deviation hence the formulations did not show any susceptible changes. The average weight of different transdermal patch formulations ranged from 30.33±1.156 to 32.66±1.165 mg. All the formulations were found to be having satisfactory results and have low standard deviation values within a formulation. The folding endurance of the patches was reported to be 75-80 to 98-99. The patches TP3 and TP4 formulations having an intermediate concentration of PVA and PVP were found to be having the satisfactory results. This ability to retain the structural integrity helps the patch to be retained over the skin surface for a longer time without breaking. The tensile strength of the patches was found to be 4.79±0.23 to 9.13±0.13 N/mm^2. It was concluded that the tensile strength decreases as the increase of Polyvinyl pyrrolidone polymer due to the anti-nucleating effect of PVP polymer. The swelling studies of all formulations were found to be a function of polymeric solution. The % swelling ranged from 16.97± 0.43 to 28.63 ± 0.54 % for all prepared formulations due to the pore forming nature of PVP polymer. Polyvinylpyrrolidone leaches out during preparation of patches from membrane casting, leaving pores typically from 1 to 10 µm. The proposed prepared patches were kept in distilled water and surface pH ranges found to be between 5.5 ± 0.13 to 5.8± 0.12 for all the formulations which is skin pH and no skin irritation. The drug content of different transdermal patches was found to be 71.23±0.3 to 80.08±1.07. The drug retained within the patch was comparatively high for LTP4 formulation. The drug content of the prepared formulations has shown that the process employed to prepare transdermal patch in this study was capable of patch with a uniform drug content and minimum batch variability. Homogeneous uniform drug distribution is one of the important characteristics of a transdermal patch that ensures the uniform reproducible sustained release of the drug from the patch. Estimation of drug content indicated that the drug is uniformly distributed throughout the patches, evidenced by the low values of the Standard Deviations. The in-vitro drug diffusion perfusion profile and release kinetics studies all prepared lamotrigene liposomal transdermal patch novel dosage forms was the important criteria, which significant the other physical characteristics to justify the optimized formulation. These parameters were played an important role for describing dissolution profile and diffusion kinetic nature of dosage form. The dissolution data was obtained after in-vitro release performance, fitted to mathematical different models. The formulations TP4 showed the values of n> 0.5, followed Fickinan diffusion and supercase II transport mechanism (Figure 4). The value of t50% of TP4 was indicated more than 6 h and was retarded drug release upto 90% till 12h to get better controlled drug release profile. it was shown better controlled release mechanism of prepared drug delivery system.

Table 1: Formulation composition of liposomes

S. No.	Formulation code	Drug (mg)	Soyalecithin (mg)	Cholesterol (mg)	Stirring Speed (rpm)
1	LLP1	100	100	20	200
2	LLP2	100	100	40	200
3	LLP3	100	100	20	100
4	LLP4	100	100	40	100

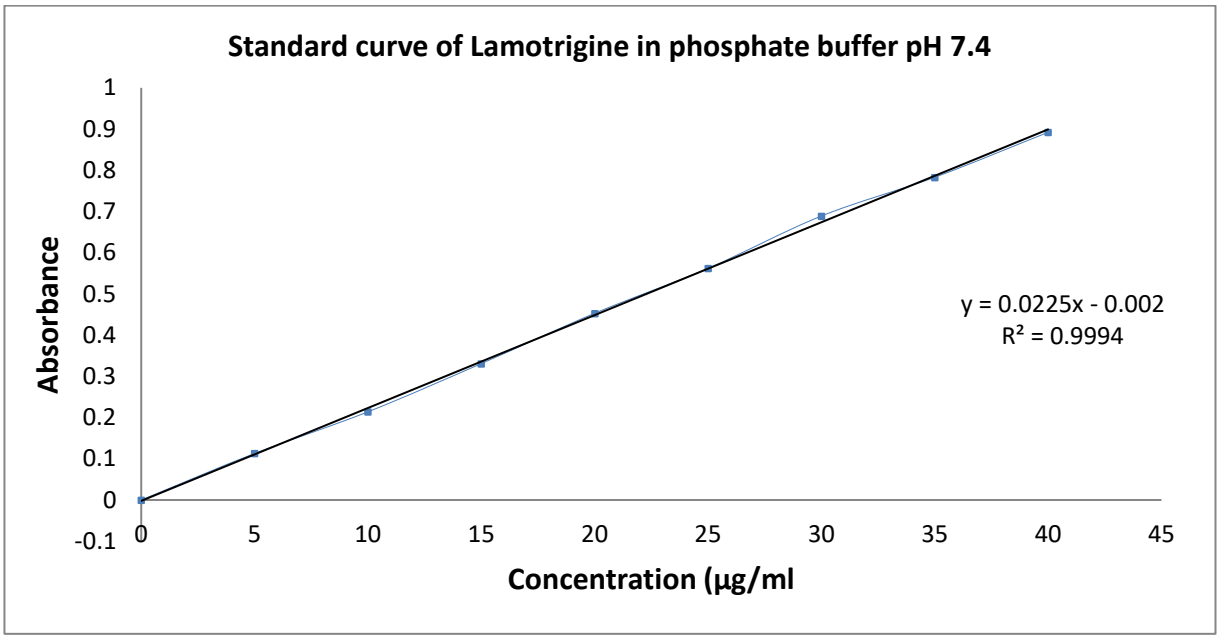

Figure 1: Standard curve of Lamotrigine in phosphate buffer pH 7.4 (305 nm)

Table 2: Optimization parameters of various formulations of liposomes

S. No.	Formulation code	Particle size (nm)	Layers	Zeta potential (mV)	PDI	Drug Entrapment (%)
1	LLP1	122.11±1.12	Single	-20.12±1.02	0.226±0.11	63.05±0.8
2	LLP2	124.13±1.04	Single	-20.21±1.11	0.226±0.08	68.32±1.2
3	LLP3	130.11±1.09	Double	-22.24±1.04	0.229±0.01	65.12±1.2
4	LLP4	131.31±1.08	Double	-22.78±1.08	0.228±0.07	71.86±1.1

Results

		Diam. (nm)	% Intensity	Width (nm)
Z-Average (d.nm): 131.31	Peak 1:	132	99.11	51
PdI: 0.228	Peak 2:	0.00	0.0	0.00
Intercept: 0.304	Peak 3:	0.00	0.0	0.00

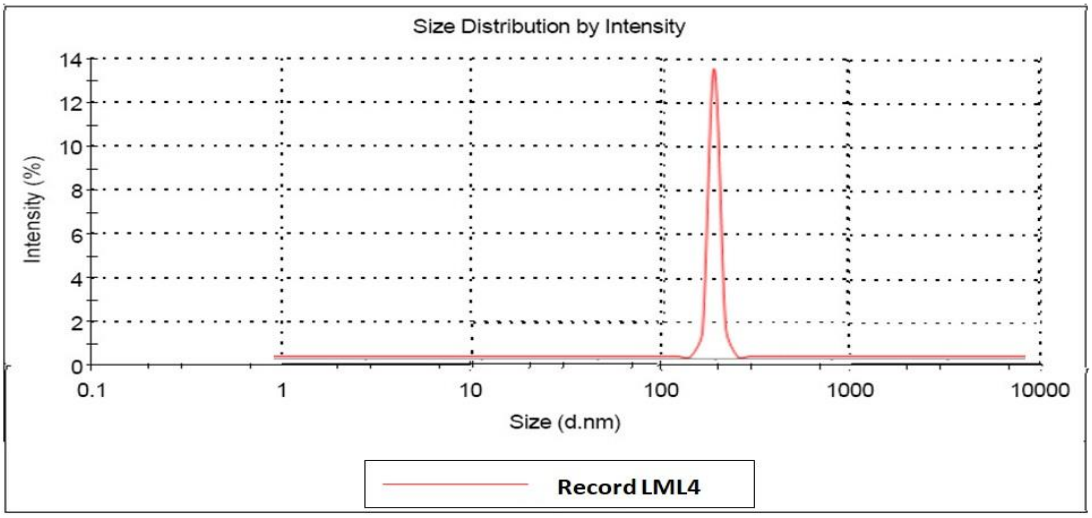

Figure 2: Particle size distribution & Polydispersity Index (PDI) of liposomes (LLP4)

Results

		Mean (mV)	Area (%)	Width (mV)
Zeta Potential (mV):-22.78	Peak 1:-22.78		93	3.16
Zeta Deviation (mV): 58.44	Peak 2: 0.00		0.0	0.00
Conductivity (mS/cm): 0.312	Peak 3: 0.00		0.0	0.00

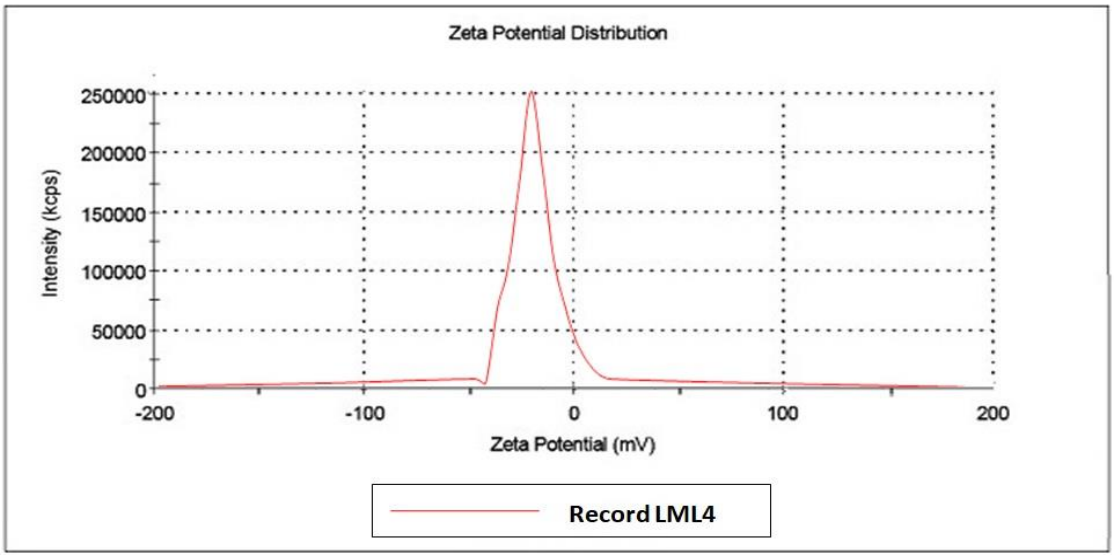

Figure 3: Zeta potential (mV) of liposomes (LLP4)

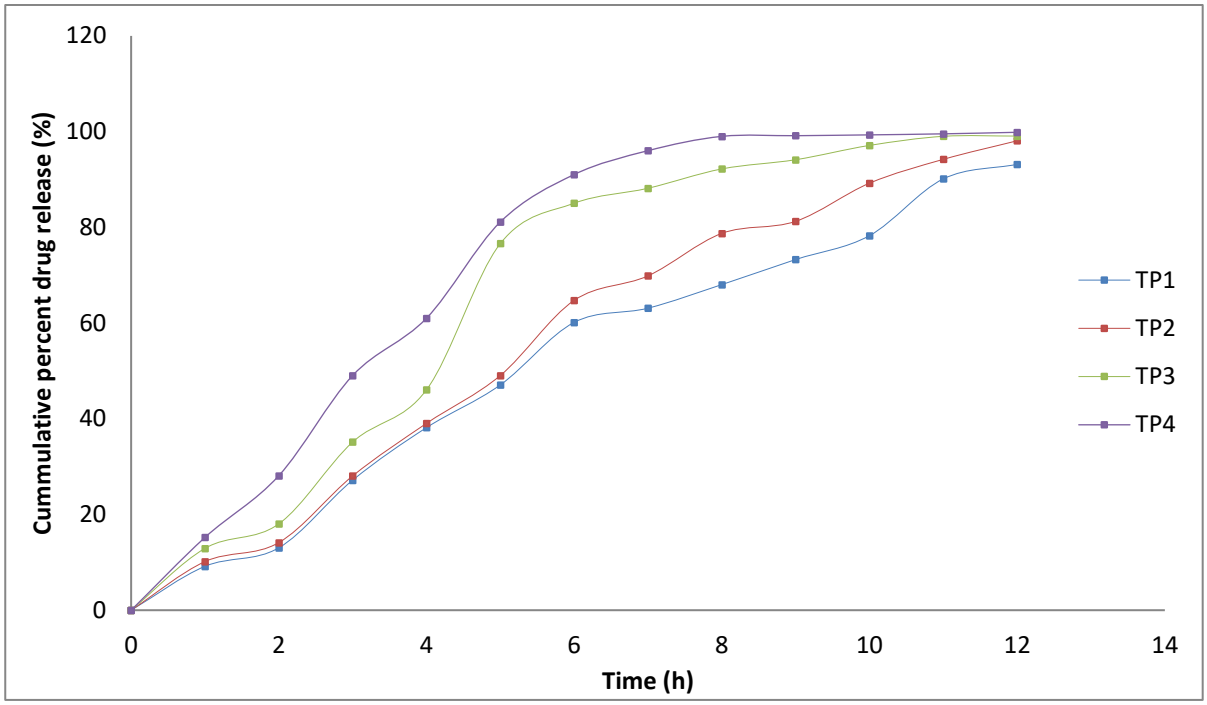

Figure 4: Zero-order plots of liposomes transdermal patch formulation (TP1 –TP4)

SUMMARY AND CONCLUSION:

These patients may have difficulty in swallowing, may be in coma or may have gastrointestinal discomfort. Patient compliance may be a problem for those who cannot tolerate the taste of oral medications. Additionally, polypharmacy can be an issue, especially in the elderly population, causing noncompliance and forgetfulness due to the requirement of frequent dosing. Conventionally, transdermal drug delivery research is usually restricted to low-dose, potent compounds with optimal physicochemical properties. Recently, though, more research laboratories are devoting considerable time and effort to the development of transdermal drug delivery systems for high dose compounds. The proportion of PVP with PVA is responsible for better cumulative release among the formulations. High hydrophilicity of polymers resulted in increase in absorbion of water and incresase in percentage swelling resulting in the more release of drug from the patches. Release rate of drugs from the PVA: PVP having penetration enhancer Propylene Glycol 400 and Tween 80 and **TP4** is the best formulation in this combination. The percent of drug permeated in 12 h was found to be maximum 99.86 % from formulations **TP4**. The data was further treated as per the following equation for confirming the Koresmeyer-Peppas model, Where, Mt / Mα, was the fractional release of drug, Mt is the amount released at time t, Mα is the total amount of drug contained in the transdermal patch, t is the release time, K is a kinetic constant and the diffusional release exponent indicative of the release mechanism. The formulations **TP4** showed the values of n>0.5, it means drug permeation followed Fickian diffusion.

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